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# The reproductive number for an HIV model with differential infectivity and staged progression ☆

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**Abstract**

We formulate an HIV epidemic model with differential infectivity and staged disease progression to account for variations in viral loads and in the rate of disease progression in infected individuals. The stability of the infection-free equilibrium determines the threshold conditions under which the modeled disease either dies out or persists in the population. This stability, expressed in terms of the epidemic reproductive number, can be determined by the spectral radius of the next generation operator, or from the eigenvalues of the Jacobian matrix for the model system linearized about the infection-free equilibrium. We derive an explicit formula for the reproductive number employing both of these techniques by investigating the spectral radius of the next generation operator, and by directly applying M-matrix theory with recursive forward and backward inductions to characterize the eigenvalues of the Jacobian matrix in terms of the reproductive number.


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## 1. Introduction

Mathematical models for the spread of HIV, based on the mechanisms of the transmission process, lead to a deeper understanding of the future spread of disease because explicit elements of biology and behavior are included in the models. These elements can affect the future course of the epidemic, and the effects will be highly nonlinear functions of the parameter values. At times the models may even predict changes that are counter to both intuition and simple extrapolated predictions.

In the studies of the transmission dynamics of HIV, two fundamental hypotheses for variations in infectiousness have been employed. In the staged-progression (SP) hypothesis, the infected individuals sequentially pass through a series of stages, being highly infectious in the first few weeks after their own infection, then having low infectivity for many years, and finally becoming gradually more infectious as their immune system breaks down and they progress to AIDS [1,11,25]. Both deterministic and statistic SP models have been formulated and studied to understand the impact of the disease progression on the spread of HIV [2,19–22,26,28]. Based on other clinic findings and blood serum level studies [3,6,18], another hypothesis is the differential infectivity (DI) hypothesis, where infected individuals enter one of several groups, depending on their infectivity, and stay in that group until they develop AIDS [12].

Analytic and numerical comparisons between the dynamics of the SP and the DI models [12] show that the long-term asymptotic transmission dynamics for both models are completely determined by the reproductive number; that is, at the endemic equilibrium the fractions of the susceptible and infected individuals in the population are simply expressed in terms of the reproductive number. However, even when the two models had the same reproductive number, the same endemic equilibrium, and similar initial infection status, their transient transmission dynamics are quite different. These differences indicate that using the correct hypothesis in the mathematical model is crucial for better understanding of the transmission of an epidemic.

The sensitivity of the epidemics in the DI and SP models to factors such as infectiousness and migration, and the impact of partner notification and screening programs on the spread of infection were studied further in [13,15]. However, these studies left a number of questions unanswered about how best to control the spread of infection, which can only be addressed by a full model that incorporates aspects of both temporal (SP) and individual (DI) variations in infectiousness.

In this paper, we combine the SP and DI hypotheses to formulate and analyze a DISP model that incorporates variations among individuals (DI) and in the disease progression (SP).

One of the fundamental questions of mathematical epidemiology is to find threshold conditions that determine whether an infectious disease will spread in a suscep-

tible population when the disease is introduced into the population. The threshold conditions are characterized by the so-called reproductive number, the basic reproduction number, or the reproductive ratio, commonly denoted by $R_0$, in mathematical epidemiology [7,10,17,27]. The reproductive number is defined such that if $R_0 < 1$, the modeled disease dies out if a small infection is introduced into a susceptible population, and if $R_0 > 1$, the disease spreads in the population.

The reproductive number is usually defined by the spectral radius of the next generation operator [7,8,16,27]. It can also be determined by the dominant eigenvalue of the Jacobian matrix at the infection-free equilibrium for models in a finite dimensional space [14,24]. We use both of these techniques to derive an explicit formula for the reproductive number of infection for the DISP model in this paper.

We determine the spectral radius of the next generation operator and demonstrate that this approach gives the same reproductive number as the approach based on direct applications of M-matrix theory and recursive forward and backward inductions, to investigate the eigenvalues of the Jacobian matrix of the model equations at the infection-free equilibrium. The applications of M-matrix theory and linear algebra to the derivation of the reproductive number for the DISP model demonstrate that linear algebra is key to solving various applied problems.

## 2. The DISP Model Formulation

We assume in the DISP model, shown in Fig. 1, that the population is homogeneous except in its response to HIV infection. In the absence of infection, the population of susceptible individuals, $S$, has a constant steady state, $S^0$, via a constant inflow and outflow, where each individual remains in the population an average of $\mu^{-1}$ years; thus $\mu$ is the removal rate due to natural death in the absence of HIV infection, migration, and changes in sexual behavior. Individuals are infected by HIV at a per capita rate $\lambda$.

The infected population is divided into $n$ groups such that individuals in each group have the same infectivity, but those from different groups have differential infectivities. The group that an individual belongs to upon infection is determined by the individual's physiology and/or the HIV virus infecting him/her. We assume that this infection group is not a transmissible property of the HIV virus, since there is no solid evidence that the individuals infected by an individual who is more infectious than others in the same population (and thus carrying closely-related versions of HIV) are themselves more infectious (or vice versa). The fraction $p_i$ of the newly infectives, where $\sum_{i=1}^{n} p_i = 1$, go into the $i$th group, and stay in this group until they leave the high-risk population because of behavior changes that are induced by either HIV-related illnesses or a positive HIV test and the subsequent desire not to transmit infection. We denote this subgroup of removed individuals by $A$.

We further assume that each group $i$ of the infected population is subdivided into $m$ subgroups, $I_{i,1}, I_{i,2}, \ldots, I_{i,m}$, with different infection stages such that infected

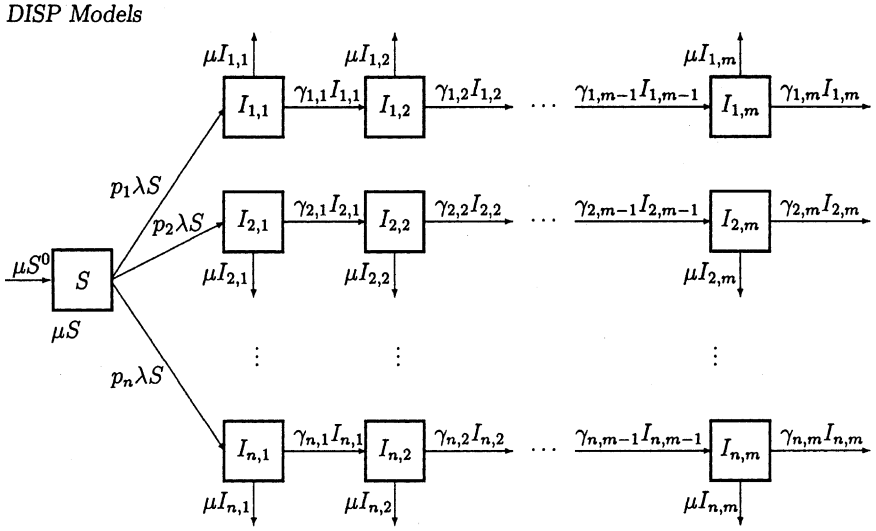


Fig. 1. In this DISP model, when a susceptible is infected, this individual enters one of the infection groups $I_{i,1}$ with probability $p_i$. Each infection group progresses through a series of stages where the progression rates $\gamma_{i,j}$ and infectivity $\beta_{i,j}$ vary. Since the transmission caused by individuals in group $A$ is neglected, group $A$ is not shown in this schematic diagram.

susceptible individuals enter the first subgroup $I_{i,1}$ and then gradually progress from subgroup $I_{i,1}$ finally to subgroup $I_{i,m}$. Let $\gamma_{i,k}$ be the average rate of progression from subgroup $I_{i,k}$ to subgroup $I_{i,k+1}$, for $k = 1, \ldots, m-1$, and $\gamma_{i,m}$ be the rate at which infectives in subgroup $I_{i,m}$ enter the removed population, $A$. The rate of leaving the high risk population and entering the removed population may depend on the index $i$ because there may be a link between the amount of viral shedding and how quickly an individual becomes sick. People in $A$ are assumed to have a higher removal rate $\delta \geqslant \mu$, where $\mu$ accounts for both natural death in the absence of HIV infection and migration in and out of the susceptible population.

We neglect transmission by the $A$ group, under the assumption that individuals in this group have significantly reduced their sexual activity or infectivity such that the transmission caused by them is negligible compared to the rest of the infected population. Then the dynamics of the DISP model are governed by the following equations:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu(S^0 - S) - \lambda S, \\
\frac{\mathrm{d}I_{i,1}}{\mathrm{d}t} &= p_i\lambda S - (\mu + \gamma_{i,1})I_{i,1}, \quad i = 1, \ldots, n, \\
\frac{\mathrm{d}I_{i,k}}{\mathrm{d}t} &= \gamma_{i,k-1}I_{i,k-1} - (\mu + \gamma_{i,k})I_{i,k}, \quad i = 1, \ldots, n, \quad k = 2, \ldots, m, \\
\frac{\mathrm{d}A}{\mathrm{d}t} &= \sum_{i=1}^{n} \gamma_{i,m}I_{i,m} - \delta A.
\end{aligned} \tag{2.1}$$

The rate of infection, $\lambda$, depends on the product of the infectivity or the transmission probability per contact, $\beta_{i,k}$, of individuals in group $i$ during the $k$th infection stage, the proportion of the population in the subgroup, $I_{i,k}/N$, and the number of contacts of an individual per unit of time, $r$. We assume that the $r$ contacts are randomly distributed over the whole population so that

$$\lambda = r \sum_{i=1}^{n} \sum_{k=1}^{m} \beta_{i,k} \frac{I_{i,k}}{N}, \tag{2.2}$$

where $N := S + \sum_{i=1}^{n} \sum_{k=1}^{m} I_{i,k}$ is the total number of sexually active individuals in the population.

## 3. The reproductive number of infection

We note that since the transmission by AIDS cases has been neglected under our assumptions, the transmission dynamics of (2.1) are determined by the transmission dynamics of the susceptibles and infectives. We ignore the equation for group $A$ hereafter, and derive an explicit formula for the reproductive number of the system using two different techniques in the following two sections.

### *3.1. Spectral radius of the next generation operator*

We first derive an explicit formula for the reproductive number of infection by determining the spectral radius of the next generation operator of system (2.1) with (2.2) as follows.

System (2.1) has an infection-free equilibrium, given by ($S = S^0$, $I_{i,j} = 0$, $i = 1, \ldots, n$, $j = 1, \ldots, m$). Linearizing system (2.1) around the infection-free equilibrium, we have the following Jacobian matrix:

$$J_{n,m} := \begin{pmatrix} -\mu & \cdot & \cdot & \cdot & \cdot & \cdots & \cdot & \cdot \\ 0 & P_{1,1} + D_{1,1} & P_{1,2} & P_{1,3} & P_{1,4} & \cdots & P_{1,m-1} & P_{1,m} \\ 0 & D_{2,1} & D_{2,2} & 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & D_{3,2} & D_{3,3} & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \cdots & D_{m,m-1} & D_{m,m} \end{pmatrix}, \tag{3.1}$$

where

$$P_{1,j} := \begin{pmatrix} p_1 r \beta_{1,j} & p_1 r \beta_{2,j} & \cdots & p_1 r \beta_{n,j} \\ \vdots & \vdots & \ddots & \vdots \\ p_n r \beta_{1,j} & p_n r \beta_{2,j} & \cdots & p_n r \beta_{n,j} \end{pmatrix}, \quad j = 1, \ldots, m,$$

$$D_{j,j} := \begin{pmatrix} -\sigma_{1,j} & \cdots & 0 \\ \vdots & \ddots & 0 \\ 0 & \cdots & -\sigma_{n,j} \end{pmatrix}, \quad j = 1, \ldots, m, \tag{3.2}$$

and

$$D_{j,j-1} := \begin{pmatrix} \gamma_{1,j-1} & \cdots & 0 \\ \vdots & \ddots & 0 \\ 0 & \cdots & \gamma_{n,j-1} \end{pmatrix}, \quad j = 2, \ldots, m, \tag{3.3}$$

with $\sigma_{i,j} = \mu + \gamma_{i,j}$.

Employing the technique developed in [7,8,27], we only consider the entries in $J_{n,m}$ that are from infective equations $\mathrm{d}I_{i,j}/\mathrm{d}t$ and use the same notations as in [27]. Define matrices $F$ and $V$ as

$$F := \begin{pmatrix} P_{1,1} & P_{1,2} & P_{1,3} & \cdots & P_{1,m} \\ 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & 0 \end{pmatrix},$$

$$V := \begin{pmatrix} -D_{1,1} & 0 & 0 & \cdots & 0 & 0 \\ -D_{2,1} & -D_{2,2} & 0 & \cdots & 0 & 0 \\ 0 & -D_{3,2} & -D_{3,3} & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & -D_{m-1,m-1} & 0 \\ 0 & 0 & 0 & \cdots & -D_{m,m-1} & -D_{m,m} \end{pmatrix}. \tag{3.4}$$

Then $F$ is a nonnegative matrix and $V$ is a nonsingular M-matrix. Hence the reproductive number, $R_0$, is equal to the spectral radius of the next generation operator $FV^{-1}$ [27]:

$$R_0 = \rho(FV^{-1}).$$

To determine the spectral radius of $FV^{-1}$, we first represent the inverse of $V$ by the following lower triangular matrix:

$$V^{-1} = \begin{pmatrix} V_{11} & 0 & \cdots & 0 \\ V_{2,1} & V_{2,2} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ V_{m,1} & V_{m,2} & \cdots & V_{m,m} \end{pmatrix},$$

where

$$V_{i,i} = -D_{i,i}^{-1}, \quad i = 1, \ldots, m,$$

and $V_{i,j}$ are defined recursively by

$$V_{i,j} = -D_{i,i-1} V_{i-1,j} D_{i,i}^{-1}, \quad i = 2, \ldots, m, \quad j < i. \tag{3.5}$$

In fact, because every diagonal submatrix of $VV^{-1}$ is an identity matrix, we only consider an arbitrary $(i, j)$-submatrix of $VV^{-1}$ for $j < i$. Notice that $D_{i,j}$ are all $n \times n$ diagonal matrices. Matrices $D_{i,j}$ and $D_{i,j}^{-1}$ are all commutative. Hence

$$\begin{aligned} -D_{i,i-1}V_{i-1,j} - D_{i,i}V_{i,j} &= -D_{i,i-1}V_{i-1,j} + D_{i,i}D_{i,i-1}V_{i-1,j}D_{i,i}^{-1} \\ &= -D_{i,i-1}V_{i-1,j} + D_{i,i-1}V_{i-1,j} = 0. \end{aligned}$$

Since $-D_{i,i-1}$ and $-D_{i,i}$ are the only nonzero submatrices on row $i$, for $i = 2, \ldots, m$, in $V$, every $(i, j)$-submatrix of $VV^{-1}$ for $j < i$ is a zero matrix.

Now we are ready to derive an explicit formula for the reproductive number $R_0$. Since matrix $F$ has rank 1, the spectral radius $\rho(FV^{-1})$ is equal to the trace of matrix $FV^{-1}$. Note that the only nonzero submatrices of $F$ are $P_{1,i}$. Then

$$\text{trace } FV^{-1} = \text{trace} \sum_{i=1}^{m} P_{1,i}V_{i,1}.$$

Using the recursive formula (3.5), we have

$$V_{i,1} = (-1)^i \prod_{k=2}^{i} D_{k,k-1} \prod_{k=1}^{i} D_{k,k}^{-1}, \tag{3.6}$$

which can be shown by induction as follows.

Given that

$$V_{1,1} = -D_{1,1}^{-1} = (-1)^1 \prod_{k=2}^{1} D_{k,k-1} \prod_{k=1}^{1} D_{k,k}^{-1},$$

(3.6) holds for $i = 1$. Suppose (3.6) holds for $i$. It follows from (3.5) and (3.6) that

$$\begin{aligned} V_{i+1,1} &= -D_{i+1,i}V_{i,1}D_{i+1,i+1}^{-1} = (-1)^{i+1}D_{i+1,i} \prod_{k=2}^{i} D_{k,k-1} \prod_{k=1}^{i} D_{k,k}^{-1} D_{i+1,i+1}^{-1} \\ &= (-1)^{i+1} \prod_{k=2}^{i+1} D_{k,k-1} \prod_{k=1}^{i+1} D_{k,k}^{-1}. \end{aligned}$$

Hence (3.6) holds for $i + 1$, and therefore holds for all $i = 1, \ldots, m$.

Substituting $D_{k,k-1}$ and $D_{k,k}$ given in (3.2) and (3.3) into (3.6), we have

$$\begin{aligned} V_{i,1} = (-1)^i \text{diag} &\left( \prod_{k=2}^{i} \gamma_{1,k-1}, \ldots, \prod_{k=2}^{i} \gamma_{n,k-1} \right) \\ \times (-1)^i \text{diag} &\left( \prod_{k=1}^{i} \sigma_{1,k}^{-1}, \ldots, \prod_{k=1}^{i} \sigma_{n,k}^{-1} \right) \end{aligned}$$

$$= \operatorname{diag}\left(\frac{1}{\sigma_{1,i}}\prod_{k=1}^{i-1}\frac{\gamma_{1,k}}{\sigma_{1,k}}, \ldots, \frac{1}{\sigma_{n,i}}\prod_{k=1}^{i-1}\frac{\gamma_{n,k}}{\sigma_{n,k}}\right).$$

The diagonal entries of $P_{1,i}V_{i,1}$ are

$$p_j r \frac{\beta_{j,i}}{\sigma_{j,i}}\prod_{k=1}^{i-1}\frac{\gamma_{j,k}}{\sigma_{j,k}}, \quad j = 1, \ldots, n.$$

Therefore

$$\text{trace } FV^{-1} = \text{trace} \sum_{i=1}^{m} P_{1,i}V_{i,1} = r\sum_{j=1}^{n} p_j \sum_{i=1}^{m}\frac{\beta_{j,i}}{\sigma_{j,i}}\prod_{k=1}^{i-1}\frac{\gamma_{j,k}}{\sigma_{j,k}}.$$

In summary, we have the following theorem:

**Theorem 3.1.** *Define the reproductive number $R_0$ as*

$$\begin{aligned} R_0 &:= r\sum_{j=1}^{n} p_j \sum_{i=1}^{m}\frac{\beta_{j,i}}{\sigma_{j,i}}\prod_{k=1}^{i-1}\frac{\gamma_{j,k}}{\sigma_{j,k}} \\ &= r\sum_{j=1}^{n} p_j \sum_{i=1}^{m}\frac{\beta_{j,i}}{\mu+\gamma_{j,i}}\prod_{k=1}^{i-1}\frac{\gamma_{j,k}}{\mu+\gamma_{j,k}}. \end{aligned} \tag{3.7}$$

*If $R_0 < 1$ the infection-free equilibrium is locally asymptotically stable, and if $R_0 > 1$ the infection-free equilibrium is unstable.*

For simple mathematical epidemiological models, the formula for $R_0$ can be interpreted as the product of the number of contacts per unit of time, the infectivity of infection, and the duration of infection.

For the more sophisticated DISP model (2.1), the explicit formula (3.7) for the reproductive number $R_0$ can also be interpreted as the product of the mean number of contacts per unit of time, the total mean infectivity of infection, and the total mean duration of infection.

We set

$$q_{j,i} := \prod_{k=1}^{i-1}\frac{\gamma_{j,k}}{\mu+\gamma_{j,k}},$$

which is the total probability that an infected individual with infectivity $j$ survives to infection stage $i$, and define the mean duration of infection in each staged-progression-chain as

$$\bar{\tau}_j := \sum_{i=1}^{m}\frac{q_{j,i}}{\mu+\gamma_{j,i}}, \quad j = 1, 2, \ldots, n.$$

Then, the total mean duration of infection for the DISP model is

$$\bar{\tau} := \sum_{j=1}^{n} p_j \bar{\tau}_j.$$

Define the mean infectivity for each staged-progression-chain as

$$\bar{\beta}_j := \frac{1}{\bar{\tau}_j} \sum_{i=1}^{m} \frac{\beta_{j,i} q_{j,i}}{\mu + \gamma_{j,i}}.$$

Then, the total mean infectivity of infection for the DISP model is

$$\bar{\beta} := \frac{1}{\bar{\tau}} \sum_{j=1}^{n} p_j \bar{\beta}_j \bar{\tau}_j.$$

Therefore, the reproductive number $R_0$ can be rewritten as

$$R_0 = r\bar{\beta}\bar{\tau}.$$

### 3.2. Eigenvalues of the Jacobian matrix

We have derived the explicit formula for $R_0$ in (3.7) using the technique of the next generation operator. Because all entries of matrices $D_{i,j}$ are nonnegative for $i \neq j$, we can also derive the formula for $R_0$ in (3.7) by establishing local stability conditions for the infection-free equilibrium directly applying M-matrix theory to matrix $J_{n,m}$ to locate the eigenvalues of $J_{n,m}$. We provide a detailed proof in this section.

Recall from well-known results of M-matrix theory that if $B = [b_{ij}]$ is an irreducible $n \times n$ matrix with $b_{ii} \geqslant 0$, and $b_{ij} \leqslant 0$, for $i \neq j$, $i, j = 1, \ldots, n$, then the real part of each nonzero eigenvalue of $B$ is positive if and only if there exists a positive vector $x > 0$ such that $Bx \geqslant 0$ [4,9,23].

To apply the criterion to our system, we let matrix $B = -J_{n,m}$. Then all off-diagonal entries of $B$ are nonpositive. Define the positive vector

$$W := (w_{11}, \ldots, w_{1n}, \ldots, w_{m1}, \ldots, w_{mn})^{\mathrm{T}},$$

where

$$w_{ij} := \frac{p_j \prod_{k=1}^{i-1} \gamma_{j,k}}{p_1 \prod_{k=1}^{i} \sigma_{j,k}}, \quad i = 1, \ldots, m,\ j = 1, \ldots, n,$$

with $\prod_{k=1}^{0} \gamma_{j,k} = 1$, by convention. If $R_0 < 1$,

$$B \cdot W = \left(1 - R_0, \frac{p_2}{p_1}(1 - R_0), \ldots, \frac{p_n}{p_1}(1 - R_0), 0, \ldots, 0\right)^{\mathrm{T}} \geqslant 0.$$

Hence each nonzero eigenvalue of $B$ has positive real part; that is, each nonzero eigenvalue of $J_{n,m}$ has negative real part.

To show that matrix $J_{n,m}$ has no zero eigenvalue and to complete the proof of the formula for $R_0$ in (3.7), we explicitly compute the determinant of $J_{n,m}$ as follows.

Denote the determinant of $J_{n,m}$ by $|J_{n,m}|$. By adding the first row of $J_{n,m}$ multiplied by $-p_j/p_1$ to the $j$th row, for $j = 2, \ldots, n$, respectively, $|J_{n,m}|$ equals the determinant of the matrix:

$$\Lambda_{n,m} := \begin{pmatrix} E_{1,1} & E_{1,2} & E_{1,3} & \cdots & E_{1,m-1} & E_{1,m} \\ D_{2,1} & D_{2,2} & 0 & \cdots & 0 & 0 \\ 0 & D_{3,2} & D_{3,3} & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & D_{m,m-1} & D_{m,m} \end{pmatrix},$$

where

$$E_{1,1} := \begin{pmatrix} p_1 r\beta_{1,1} - \sigma_{1,1} & p_1 r\beta_{2,1} & p_1 r\beta_{3,1} & \cdots & p_1 r\beta_{n,1} \\ \frac{p_2}{p_1}\sigma_{1,1} & -\sigma_{2,1} & 0 & \cdots & 0 \\ \frac{p_3}{p_1}\sigma_{1,1} & 0 & -\sigma_{3,1} & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \frac{p_n}{p_1}\sigma_{1,1} & 0 & 0 & \cdots & -\sigma_{n,1} \end{pmatrix},$$

$$E_{1,j} := \begin{pmatrix} p_1 r\beta_{1,j} & p_1 r\beta_{2,j} & \cdots & p_1 r\beta_{n,j} \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 \end{pmatrix}, \quad j = 2, \ldots, m.$$

We define the matrix

$$L := \begin{pmatrix} I & T_2 & T_3 & \cdots & T_m \\ 0 & I & 0 & \cdots & 0 \\ 0 & 0 & I & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & I \end{pmatrix},$$

where the matrices $I$'s are identity matrices with corresponding ranks. Multiplying $\Lambda_{n,m}$ by $L$ on the left, we have $L\Lambda_{n,m}$ equal

$$\begin{pmatrix} E_{1,1} + T_2 D_{2,1} & E_{1,2} + T_2 D_{2,2} + T_3 D_{3,2} & E_{1,3} + T_3 D_{3,3} + T_4 D_{4,3} & \cdots & E_{1,m} + T_m D_{m,m} \\ D_{2,1} & D_{2,2} & 0 & \cdots & 0 \\ 0 & D_{3,2} & D_{3,3} & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & D_{m,m} \end{pmatrix}.$$

Then, $|J_{n,m}| = |\Lambda_{n,m}| = |L\Lambda_{n,m}|$. Hence to obtain $|J_{n,m}|$, we only need to compute $|L\Lambda_{n,m}|$.

To simplify the computation of $|L\Lambda_{n,m}|$, we use particular representations for the entries $T_i$, $i = 1, \ldots, m$, in matrix $L$. We first establish the following lemmas.

**Lemma 3.2.** *Let matrices $T_i$ satisfy*

$$E_{1,m} + T_m D_{m,m} = 0, \tag{3.8}$$

$$E_{1,i} + T_i D_{i,i} + T_{i+1} D_{i+1,i} = 0, \quad 2 \leqslant i \leqslant m-1. \tag{3.9}$$

*Then*

$$T_i = \left( \sum_{j=i}^{m} (-1)^{j+1-i} E_{1,j} \prod_{k=1}^{j-i} (D_{i+k,i+k})^{-1} D_{i+k,i+k-1} \right) (D_{i,i})^{-1}$$
$$i = 2, \ldots, m, \tag{3.10}$$

*where $\prod_{k=1}^{0} (D_{i+k,i+k})^{-1} = I$, the identity matrix, for each $i$, by convention.*

**Proof.** We prove (3.10) by backward induction.

If $i = m$, it follows from (3.8) that

$$\begin{aligned} T_m &= -E_{1,m} (D_{m,m})^{-1} \\ &= \left( \sum_{j=m}^{m} (-1)^{j+1-m} E_{1,j} \prod_{k=1}^{j-m} (D_{m+k,m+k})^{-1} D_{m+k,m+k-1} \right) (D_{m,m})^{-1}. \end{aligned}$$

Hence (3.10) holds.

Suppose (3.10) holds for any $i+1$, $i \leqslant m-1$. We show (3.10) holds for $i$. It follows from (3.9) that

$$T_i = -E_{1,i} (D_{i,i})^{-1} - T_{i+1} D_{i+1,i} (D_{i,i})^{-1}. \tag{3.11}$$

By induction assumption,

$$\begin{aligned} &-T_{i+1} D_{i+1,i} (D_{i,i})^{-1} \\ &= \left( \sum_{j=i+1}^{m} (-1)^{j+1-i} E_{1,j} \prod_{k=1}^{j-i-1} (D_{i+1+k,i+1+k})^{-1} D_{i+1+k,i+k} (D_{i+1,i+1})^{-1} \right) \\ &\quad \times D_{i+1,i} (D_{i,i})^{-1} \\ &= \sum_{j=i+1}^{m} (-1)^{j+1-i} E_{1,j} \left( \prod_{k=2}^{j-i} (D_{i+k,i+k})^{-1} D_{i+k,i+k-1} \right) \\ &\quad \times \left( (D_{i+1,i+1})^{-1} D_{i+1,i} \right) (D_{i,i})^{-1} \end{aligned}$$

$$= \left( \sum_{j=i+1}^{m} (-1)^{j+1-i} E_{1,j} \prod_{k=1}^{j-i} (D_{i+k,i+k})^{-1} D_{i+k,i+k-1} \right) (D_{i,i})^{-1}. \tag{3.12}$$

We can rewrite

$$-E_{1,i}(D_{i,i})^{-1} = (-1)^{i+1-i} E_{1,i} \prod_{k=1}^{0} (D_{i+k,i+k})^{-1} D_{i+1,i+k-1} (D_{i,i})^{-1}, \tag{3.13}$$

by substituting (3.12) and (3.13) into (3.11). Hence equation (3.10) holds for $i$, and by backward mathematical induction, the proof is complete. □

**Lemma 3.3.** *Let the determinant $M_n$ be defined as*

$$M_n := \left| \begin{pmatrix} a_{11} - \sigma_{1,1} & a_{12} & a_{13} & \cdots & a_{1n} \\ a_{21} & -\sigma_{2,1} & 0 & \cdots & 0 \\ a_{31} & 0 & -\sigma_{3,1} & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{n1} & 0 & 0 & \cdots & -\sigma_{n,1} \end{pmatrix} \right|. \tag{3.14}$$

*Then*

$$M_n = (-1)^n \prod_{i=1}^{n} \sigma_{i,1} \left( 1 - \frac{a_{11}}{\sigma_{1,1}} - \sum_{j=2}^{n} \frac{a_{1j} a_{j1}}{\sigma_{1,1} \sigma_{j,1}} \right), \quad n \geqslant 2. \tag{3.15}$$

**Proof.** We prove the lemma by forward induction.

Note that (3.15) holds for $n = 2$. Suppose (3.15) holds for $n$. By expanding $M_{n+1}$ along the last column, we have

$$\begin{aligned} M_{n+1} &= -\sigma_{n+1,1} M_n + (-1)^n a_{1,n+1} (-1)^{n+1} a_{n+1,1} (-1)^{n-1} \prod_{i=2}^{n} \sigma_{i,1} \\ &= (-1)^{n+1} \left( \prod_{i=1}^{n+1} \sigma_{i,1} \right) \left( 1 - \frac{a_{11}}{\sigma_{1,1}} - \sum_{j=2}^{n} \frac{a_{1j} a_{j1}}{\sigma_{1,1} \sigma_{j,1}} \right) \\ &\quad -(-1)^{n+1} \left( \prod_{i=1}^{n+1} \sigma_{i,1} \right) \frac{a_{1,n+1} a_{n+1,1}}{\sigma_{1,1} \sigma_{n+1,1}} \\ &= (-1)^{n+1} \left( \prod_{i=1}^{n+1} \sigma_{i,1} \right) \left( 1 - \frac{a_{11}}{\sigma_{1,1}} - \sum_{j=2}^{n+1} \frac{a_{1j} a_{j1}}{\sigma_{1,1} \sigma_{j,1}} - \right). \end{aligned}$$

Hence (3.15) holds for $n + 1$ and therefore it holds for all $n \geqslant 2$. □

Using these lemmas, we compute the determinant of $J_{n,m}$ as follows.

**Theorem 3.4.** *The determinant of $J_{n,m}$ can be expressed as*

$$|J_{n,m}| = (-1)^{nm} \prod_{i=1}^{n} \prod_{j=1}^{m} \sigma_{i,j}(1 - R_0). \tag{3.16}$$

**Proof.** Let $T_i$, in matrix $L$, satisfy (3.8) and (3.9). Then, except the first entry, all entries in the first row are zero. Hence

$$|J_{n,m}| = |L\Lambda_{n,m}| = |E_{1,1} + T_2 D_{2,1}| \prod_{i=2}^{m} |D_{i,i}|. \tag{3.17}$$

Since

$$\begin{aligned}
&(D_{2+j,2+j})^{-1} D_{2+j,1+j} \\
&\quad = \operatorname{diag}\left(-\frac{1}{\sigma_{1,2+j}}, \ldots, -\frac{1}{\sigma_{n,2+j}}\right) \cdot \operatorname{diag}\left(\gamma_{1,1+j}, \ldots, \gamma_{n,1+j}\right) \\
&\quad = \operatorname{diag}\left(-\frac{\gamma_{1,j+1}}{\sigma_{1,j+2}}, \ldots, -\frac{\gamma_{n,j+1}}{\sigma_{n,j+2}}\right), \quad j = 0, \ldots, i-2, \\
T_2 D_{2,1} &= \sum_{i=2}^{m} (-1)^{i+1} E_{1,i} \prod_{j=1}^{i-2} (D_{2+j,2+j})^{-1} D_{2+j,1+j} (D_{2,2})^{-1} D_{2,1} \\
&\quad = \sum_{i=2}^{m} (-1)^{i+1} E_{1,i} \cdot \operatorname{diag}\left((-1)^{i-1} \frac{\prod_{j=0}^{i-2} \gamma_{1,j+1}}{\prod_{j=1}^{i-1} \sigma_{1,j+2}}, \right. \\
&\qquad \left. \ldots, (-1)^{i-1} \frac{\prod_{j=0}^{i-2} \gamma_{n,j+1}}{\prod_{j=1}^{i-1} \sigma_{n,j+2}}\right) \\
&\quad = \sum_{i=2}^{m} E_{1,i} \cdot \operatorname{diag}\left(\frac{\prod_{j=1}^{i-1} \gamma_{1,j}}{\prod_{j=1}^{i-1} \sigma_{1,j+1}}, \ldots, \frac{\prod_{j=1}^{i-1} \gamma_{n,j}}{\prod_{j=1}^{i-1} \sigma_{n,j+1}}\right).
\end{aligned} \tag{3.18}$$

Then it follows from Lemma 3.3, where we let

$$\begin{aligned}
a_{1j} &= p_1 r \left(\beta_{j,1} + \sum_{j=2}^{m} \beta_{j,i} \prod_{k=1}^{i-1} \frac{\gamma_{j,k}}{\sigma_{j,k+1}}\right), \quad 1 \leqslant j \leqslant m, \\
a_{j1} &= \frac{p_j}{p_1} \sigma_{1,1}, \quad 2 \leqslant j \leqslant m,
\end{aligned}$$

that

$$
\begin{aligned}
|E_{1,1} + T_2 D_{2,1}| &= (-1)^n \prod_{i=1}^{n} \sigma_{i,1} \left( 1 - r p_1 \sum_{j=1}^{m} \frac{\beta_{1,j}}{\sigma_{1,1}} \prod_{k=1}^{j-1} \frac{\gamma_{1,k}}{\sigma_{1,k+1}} \right. \\
&\qquad \left. - r \sum_{i=2}^{n} p_i \sum_{j=1}^{m} \frac{\beta_{i,j}}{\sigma_{i,1}} \prod_{k=1}^{j-1} \frac{\gamma_{i,k}}{\sigma_{i,k+1}} \right) \\
&= (-1)^n \prod_{i=1}^{n} \sigma_{i,1} \left( 1 - r \sum_{i=1}^{n} p_i \sum_{j=1}^{m} \frac{\beta_{i,j} \prod_{k=1}^{j-1} \gamma_{i,k}}{\prod_{k=1}^{j} \sigma_{i,k}} \right) \\
&= (-1)^n \prod_{i=1}^{n} \sigma_{i,1} (1 - R_0). \qquad (3.19)
\end{aligned}
$$

Moreover, since $|D_{i,i}| = (-1)^n \prod_{j=1}^{n} \sigma_{j,i}$, we have

$$
\begin{aligned}
|J_{n,m}| = |L \Lambda_{n,m}| &= |E_{1,1} + T_2 D_{2,1}| \prod_{i=2}^{m} |D_{i,i}| \\
&= (-1)^{nm} \prod_{i=1}^{n} \prod_{j=1}^{m} \sigma_{i,j} (1 - R_0). \qquad (3.20)
\end{aligned}
$$

The proof is complete. □

Now suppose $R_0 < 1$. As we have shown above, all nonzero eigenvalues of $J_{n,m}$ have negative real part. It follows from Lemma 3.4 that $J_{n,m}$ has no zero eigenvalues in this case. Hence, all of the eigenvalues of $J_{n,m}$ have negative real part. Then the infection-free equilibrium is locally asymptotically stable. On the other hand, suppose $R_0 > 1$. Then if the product $nm$ is an odd number, $\det J_{n,m} > 0$ which implies the product of an odd number of eigenvalues of $J_{n,m}$ is positive. Hence $J_{n,m}$ has a positive eigenvalue. If the product $nm$ is an even number, $\det J_{n,m} < 0$. Then the product of an even number of eigenvalues of $J_{n,m}$ is negative which again implies that $J_{n,m}$ has a positive eigenvalue. Hence the infection-free equilibrium is unstable if $R_0 > 1$. By directly applying M-matrix theory, we provide a different proof for Theorem 3.1.

## 4. Concluding remarks

One of the fundamental questions of mathematical epidemiology is to find threshold conditions that determine whether an infectious disease will spread in a susceptible population when the disease is introduced into this population, and the threshold conditions are usually characterized by the reproductive number $R_0$.

The reproductive number plays an important role in understanding transmission dynamics of epidemics and predicting epidemics spread. The commonly used approaches in finding a formula for the reproductive number are determining the spectral radius of the next generation operator of infection [7,8,27], or investigating the eigenvalues of the Jacobian matrix of the model system at the infection-free equilibrium [5,10,14].

For the DISP model formulated in this paper, we use both of these approaches to derive an explicit formula for the reproductive number for the model. We first determine the spectral radius of the next generation operator of infection and obtain the explicit formula in (3.7). We then give a second proof for the formula by directly applying M-matrix theory to the Jacobian matrix of the model system. In our previous studies, we have also applied M-matrix theory to other sophisticated epidemic models such as those in [12,14].

The applications of M-matrix theory and other modern linear algebra theory to mathematical epidemiological models have shown that linear algebra is key to solving complicated problems in applied mathematics. The success in applying M-matrix theory to analyze simple epidemiological models is promising. However, detailed epidemic and biological models are far more complex than the simple DISP model. It is rare when the current linear algebra techniques can be used to define explicit formulas for the reproductive number for these more sophisticated epidemiological models. The structure of the Jacobian matrices in these more complex models can help guide researchers in identifying where the advances in linear algebra theory are needed to have an impact in these applications.

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